REMARKS

Courtesies extended to Applicants' representative during the telephone interview held November 17, 2004, are acknowledged with appreciation.

In accordance with the present invention, there are provided chimeric proteins comprising a covalent fusion of at least two functional protein units, wherein each functional protein unit comprises a ligand binding domain, an optional hinge domain, a DNA binding domain, and a dimerization domain of a member of the well known and thoroughly characterized steroid/thyroid hormone nuclear receptor superfamily (see Figure A schematic below showing two functional protein units, each containing a ligand binding domain, an optional hinge domain, a DNA binding domain, and a dimerization domain, which are covalently fused into a single polypeptide molecule).

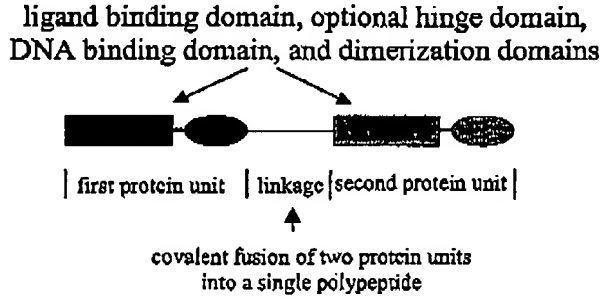

Figure A – exemplary chimeric fusion protein construct

The present claims are directed to a chimeric protein comprising at least two functional protein units. Each of these functional protein units comprises at least a ligand binding domain, an optional hinge domain, a DNA binding domain, and a dimerization domain of a member of the steroid/thyroid hormone nuclear receptor superfamily. The functional protein units form a functional entity, such that the resultant chimeric protein is biologically active. All that is required by the present claims is to make the chimeric protein comprising a fusion of at least two

functional protein units (comprising the desired functional domains as claimed) using standard molecular biological techniques for making recombinant proteins, and to test the resulting protein using functional assays, such as those taught in the working examples of the specification, to confirm that it exhibits one of the clearly identified biological functions.

By the present communication, claim 1 has been amended to define Applicants' invention with greater particularity. No new matter is introduced by the subject amendments as the amended claim language is fully supported by the specification and original claims. In addition, claims 3 and 4 have been cancelled. In view of the amendments submitted herewith, claims 1, 2, 5-11 and 13-22 remain pending. The present status of all claims in the application is provided in the Listing of Claims presented herein beginning on page 2 of this communication.

The Rejection under 35 U.S.C. § 112, First Paragraph—Enablement

The rejection of claims 1-11 and 13-22 under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to reasonably provide enablement for the chimeric proteins as claimed, is respectfully traversed. It is respectfully submitted that the present claims are fully enabled by the specification. Indeed, as acknowledged by the Examiner, "the specification . . . is enabling for a chimeric protein comprising a fusion of EcR-USP/RXR into a functional dimer" (see page 2, lines 14-16 of the Office Action).

Applicants respectfully disagree, however, with the Examiner's assertion that the specification allegedly "does not reasonably provide enablement for chimeric proteins comprising two functional protein units wherein each functional protein unit comprises the dimerization domain of a member of the steroid/thyroid hormone nuclear receptor superfamily" (see page 2, lines 16-18 of the Office Action). Contrary to the Examiner's assertion, Applicants respectfully submit that they have met the standard for enablement of the present invention. Moreover, as amended, the claims are directed to chimeric proteins comprising two functional protein units wherein each functional protein unit comprises a ligand binding domain, an optional hinge domain, a DNA binding domain, and a dimerization domain of a member of the

steroid/thyroid hormone nuclear receptor superfamily. Such chimeric proteins clearly meet the standard for enablement of the present invention.

The standard for determining enablement is whether the specification as filed provides sufficient information so as to permit one skilled in the art to make and use the claimed invention (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988)). The test of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is undue. *Id.* "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation would proceed" (*In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Indeed, a thorough evaluation of the "Wands factors" (*In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) confirms that the present claims are fully enabled.

1) The nature of the invention

The present invention is drawn to chimeric proteins comprising a covalent fusion of at least two functional protein units, wherein each functional protein unit comprises a ligand binding domain, an optional hinge domain, a DNA binding domain, and a dimerization domain of a member of the well known and thoroughly characterized steroid/thyroid hormone nuclear receptor superfamily.

2) The state of the prior art

The state of the prior art with respect to members of the steroid/thyroid hormone nuclear receptor superfamily is quite advanced, as evidenced by the reference cited by the Examiner, Aranda and Pascual, *Physiol. Rev.* **81**:1269-1304, 2001 (hereinafter referred to as "Aranda"). As previously noted, this reference is fully consistent with Applicants' assertion that the specification in fact supports enablement of the full scope of the present claims. Aranda states "[l]ike other transcriptional regulators, nuclear receptors exhibit a modular structure with different regions corresponding to autonomous functional domains that can be interchanged

between related receptors without loss of function" (emphasis added, see Aranda at page 1271, A. Domain Structure). The present claims only require that at least two such functional units are combined to form a chimeric protein that has at least one function selected from the group consisting of DNA binding, ligand binding, transactivation and dimerization. One of skill in the art could readily identify putative functional domains to utilize in the preparation of such constructs to achieve a desired function. The facts that "the exact biochemical mechanisms by which these receptors stimulate transcription are still unclear" or that "there are functional differences with the superfamily" (see page 3, lines 8-9 and 12, respectively, of the Office Action) are simply irrelevant to enablement of the present claims.

While the Examiner's extensive discussion of Aranda (see, for example, page 3, lines 6-15 of the Office Action) chooses to focus on the differences between members of the steroid/thyroid hormone nuclear receptor superfamily, the fact remains that there are far more similarities between members of the superfamily than differences. That's why they are all considered to be part of a single superfamily. If there were no differences, it wouldn't be considered a "family" of proteins.

3) The relative skill of those in the art

The relevant level of skill in the art is high.

4) The predictability or unpredictability of the art

The art of making chimeric proteins as contemplated by the present claims is predictable based on the highly developed state of the art, and the high level of skill in this field.

5) The breadth of the claims

Applicants respectfully disagree with the Examiner's assertion that "claims 1-11, 13-22 are overly broad since they encompass functional dimers comprising any member of the steroid/thyroid hormone nuclear receptor superfamily" (see page 2, lines 22-24 of the Office Action).

Contrary to the Examiner's assertion, the present claims are submitted to be of proper scope, especially as amended herein. Given the highly related nature of all members of the steroid/thyroid hormone nuclear receptor superfamily, a showing with respect to one member of the superfamily can be readily extended to other members of the superfamily.

6) The amount of direction and guidance presented

It is respectfully submitted that Applicants have provided more than a reasonable amount of guidance with respect to any experimentation required to carry out the present invention. With respect to the functional protein units, the specification teaches domains that can be used to form each functional protein unit and presents exemplary domains for use in the practice of the invention. For example, DNA binding domains are described at page 16, line 8, through page 18, line 13; ligand binding domains are described at page 14, line 26, through page 15, line 26; activation domains are described at page 18, line 14, through page 19, line 2; and dimerization domains are described at page 10, line 27, through page 11, line 18. One of skill in the art, in light of the teachings of the specification and knowledge in the art, could readily determine appropriate domains to assemble in the construction of a chimeric protein in order to achieve one or more biological functions. Moreover, Example 1 teaches the complete design and construction of exemplary chimeric fusion constructs.

7) The presence or absence of working examples

It is respectfully submitted that the working examples employ receptor members that are highly representative of the entire superfamily. Thus, additional examples with further superfamily members are clearly not necessary. Indeed, given the well characterized nature of all members of the nuclear receptor superfamily, additional examples with further superfamily members would merely be superfluous. Therefore, the claims should not be limited to just the working examples provided.

Accordingly, Applicants have provided a detailed description of important structural features required by chimeric receptors of the invention, plus functional features of such receptors. As noted above, the experimentation required would not be undue, because "time and difficulty of experiments are not determinative if they are merely routine" (MPEP §2164.06). Therefore, experiments required to characterize an inhibitor are clearly routine.

8) The quantity of experimentation necessary

Applicants respectfully disagree with the Examiner's assertion that "[i]t would require undue experimentation for one of skill in the art to make and use the claimed polypeptides." (See page 4, lines 6-7 of the Office Action). The Examiner's concern with the quantity of experimentation required to practice the present invention is respectfully submitted to be misplaced as the quantity of experimentation is only one factor involved in determining whether undue experimentation is required; moreover, time and difficulty of experiments are not determinative if they are merely routine (MPEP § 2164.06).

It is respectfully submitted that the amount of direction or guidance provided by the present specification is commensurate in scope with the claims, as amended.

Therefore, the experimentation required would not be undue, "since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation would proceed" (*In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Clearly, Applicants have provided substantial guidance on how to proceed with experimentation, as well as routine procedures and programs to do so.

For all of the reasons set forth above, it is respectfully submitted that the present claims as amended are fully enabled as required by 35 U.S.C. § 112, first paragraph. Accordingly, reconsideration and withdrawal of this rejection of claims 1-11 and 13-22 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

The Rejection under 35 U.S.C. § 112, First Paragraph—Written Description

The rejection of claims 1-11 and 13-22 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time the application was filed had possession of the claimed invention, is respectfully traversed.

Applicants respectfully disagree with the Examiner's assertion that "[n]o common structural attributes identify members of the genus." (See page 7, lines 14-15 of the Office Action). Indeed, contrary to the Examiner's incorrect assertion that "[t]he specification and claims do not indicate what distinguishing attributes [are] shared by the members of the genus" (*i.e.*, the steroid/thyroid hormone nuclear receptor superfamily; see page 7, lines 9-10 of the Office Action), this superfamily contains a remarkably uniform domain structure that was well-known in the art at the time of filing of the present application.

Applicants further disagree with the Examiner's assertion that "[t]here is no description of the conserved regions which are critical to the structure and function of the genus claimed." (See page 8, lines 5-6 of the Office Action). Since the steroid/thyroid hormone nuclear receptor superfamily is well-defined, including the ligand binding domain, optional hinge domain, DNA binding domain, and dimerization domains thereof, there is no merit to the Examiner's above-quoted concern. Moreover, Applicants are not merely relying on that which is known in the art, in addition, the specification includes extensive discussion with respect to domains that can be used to form each functional protein unit and presents exemplary domains for use in the practice of the invention. Specifically, DNA binding domains are described at page 16, line 8, through page 18, line 13; ligand binding domains are described at page 14, line 26, through page 15, line 26; activation domains are described at page 18, line 14, through page 19, line 2; and dimerization domains are described at page 10, line 27, through page 11, line 18. Clearly, the specification provides more than ample description of the conserved regions of the members of the receptor superfamily, in addition to the knowledge of one of skill in the art.

The Examiner's suggestion of information allegedly missing from the present disclosure suggests a lack of understanding of the present invention. Thus, the Examiner's suggestion that "[s]tructural features that could distinguish the compounds of the genus from other seven transmembrane region compounds are missing from the disclosure" (see page 8, lines 8-10 of the Office Action), is totally irrelevant to the present invention. The present invention relates to nuclear receptors, not transmembrane receptors.

Therefore, one of skill in the art would have no reason to doubt that Applicants were in possession of the present invention at the time of filing. Accordingly, reconsideration and withdrawal of this rejection of claims 1-11 and 13-22 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

The Rejection under 35 U.S.C. § 102(b)

The rejection of claims 1, 14, 19, 20 and 22 under 35 U.S.C. § 102(b) as allegedly being anticipated by Lees et al. (Mol Cell Biol 10:5529-31 (1990)) as evidenced by Peters et al. (Mol Endocrinol 13:286-296 (1999)), is respectfully traversed.

Applicants' invention, as defined, for example, by amended claim 1, distinguishes over Lees et al. at least by requiring a chimeric protein comprising:

> a fusion of at least two functional protein units, wherein each functional protein unit comprises a ligand binding domain, an optional hinge domain, a DNA binding domain, and a dimerization domain of a member of the steroid/thyroid hormone nuclear receptor superfamily;
>
> wherein the at least two functional protein units are covalently fused into a single polypeptide molecule by (i) fusion of the protein units, or (ii) use of a linker interposed between the protein units; and
>
> wherein the chimeric protein is capable of at least one function selected from the group consisting of DNA binding, ligand binding, transactivation and dimerization.

Lees does not disclose or suggest any such chimeric proteins. Accordingly, reconsideration and withdrawal of this rejection of claims 1, 14, 19, 20 and 22 under 35 U.S.C. § 102(b), are respectfully requested.

Conclusion

In view of the above amendments and remarks, prompt and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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